--Claim 21. The method for treating a patient having an osteoclast related bone disorder according to claim 20, wherein the bone disorder is osteoporosis.--

REMARKS

Claims 13-21 are pending in the above-identified application and stand ready for further action on the merits. Support for claims 17-21 can be found in claim 13. The amendment to claim 13 did not narrow the scope of the claim. No new matter has been added, and there is no need for a further search.

Claim Objections

Claims 14-15 stand objected to under 37 CFR 1.75(c) for failing to further limit the subject matter of a previous claim. Applicants respectfully traverse the objection.

In response, Applicants have amended claim 13 to recite the treatment of any osteoclast related bone disorder. Accordingly, Applicants respectfully submit that claims 14-15 further limit claim 13. Applicants respectfully request that the objection be withdrawn.

Issues Under 35 USC 112, Second Paragraph

Claims 14-16 stand rejected under 35 USC 112, second paragraph for being indefinite. Applicants respectfully traverse the rejection.

The Examiner objects to claims 13-15 for reciting that an "osteoclast-related bone disorder" includes prostate cancer or hormonal disorders which cannot be defined as an osteoclast-related bone disorder.

Applicants note that MPEP 2173.01 begins by stating that a

> "fundamental principle contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as the invention essentially in whatever terms they choose..."

Thus, Applicants are free to use a term such as "osteoclast-related" in the claims as long as a definition of this term is present in the specification. The specification carries a definition of this term at page 2, beginning at line 24, and at page 13, beginning at line 10, and at page 15, beginning at line 23. Accordingly, the phrase "osteoclast-related bone disorder" is

sufficiently defined in the specification to not render claims 13-15 indefinite under 35 USC 112, second paragraph.

The Examiner objects to Claim 16 as being unclear in that it recites only "units per day". The Examiner believes that it is necessary to further specify the number of units/kg. In response, Applicants respectfully submit that dosages of IFN are commonly expressed as "unit per day". See for example, S. Baron et al., The Clinical Potential of Interferons, ed. R. Kono & J. Vilcek, pp. 223-230, University of Tokyo Press, 1982. Applicants merely followed the art recognized usage.

In view of the foregoing, Applicants respectfully submit that the claims, as presently amended, particularly point out and distinctly claim what Applicants regard as the invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Issues Under 35 USC 112, First Paragraph

(A) Claim 13 stands rejected under 35 USC 112, first paragraph, because the specification, while enabling for a method of treatment of non-tumor related bone disorders, does not reasonably

provide enablement for a method of treatment of tumor related bone disorders. Applicants respectfully traverse the rejection.

In paragraph 8, the Examiner cites Sterns and Wangs (Clinical and Experimental Metastasis, 1998, Vol. 16, pp. 693-702) for teaching examples of tumors that exhibit bone solubilization action not ascribed to osteoclasts. However, the report describes in the Introduction section on page 693 that

> "Bone resorption induced by tumors may directly involve the tumor cells or arise from tumor cell dependent recruitment of osteoclasts and/or cytokine-like stimulatory effects of the tumor cells on osteoclastic osteolysis."

Similarly, Orr et al also describe in the lines 12 to 15 of the Abstract, page 2912 of Cancer, 2000, Vol. 88, pp. 2912-2918 that

> "The subsequent growth of these cells into clinically significant metastatic lesions is associated with their ability to stimulate bone resorption through osteoclasts and macrophages or through a direct action on bone".

In other words, Sterns and Wangs have proved that a bone solubilization action not mediated with osteoclasts is observed only in PC-3 ML tumor cells used in their experiments, and neither Sterns and Wangs nor Orr at al. have denied the bone

solubilization action mediated with the osteoclasts in their reports. In addition, the present Inventors ascribe novelty of the present invention with respect to the bone volume restoration effect by IFN-β to an improvement effect of relative balance between bone resorption by the osteoclasts and osteogenesis by osteoblasts, not to an antitumor effect of the tumor cells *per se*. Since Claim 13 is so constructed as to just specify the concept as described above, the rejection of Claim 13 based on the references cited by the Examiner is not tenable.

Although the Examiner has presented in paragraph 8 the report by Kloke and Niederle (Cancer Trestment Review, 1990, Vol. 17, pp. 81-88) as a basis of rejection of Claim 13, Applicants do not understand the rationale the Examiner has used in citing this reference. Applicants conjecture that the Examiner has misunderstood that the mode of action of IFN for causing the bone volume restoration effect by IFN is the tumor cells. Applicants would like to assert hereinafter that the Applicant's opinion is more appropriate over the Examiner's opinion.

Antitumor actions can be assessed by ascertaining the dosage of an agent that causes 50% depression of proliferation of the tumor cells. While this 50% depression dosage of IFN is 110

units/ml in the tumor cells having the highest sensitivity (lung cancer cells), it may exceed 10,000 units/ml in some tumor cells (N. Ida et al., GANN, 73, pp. 952-960, 1982, in Table 1, p. 954). The action on the osteoclasts may be assessed, on the other hand, by ascertaining the dosage of IFN which results in 50% depression of the generation of the osteoclasts from bone marrow calls. This depression level is 0.2 to 1.2 units/ml, as can be recognized from Figs. 1 and 2 in the Specification. The sensitivity of the osteoclasts are by 100 to 500 times higher than the highest sensitivity of the tumor cells. In other words, IFN can exert the bone volume restoration effect at a dosage where antitumor effect could be hardly expected. Accordingly, since bone diseases can be treated by IFN independently from treating tumors themselves, the problems pointed out by the Examiner never interfere with practice of the present invention.

In view of the foregoing, Applicants respectfully request that the rejection be withdrawn.

(B) Claim 16 stands rejected under 35 USC 112, first paragraph, because the specification does not describe in such a way as to

enable the skilled artisan to make and/or use the invention. Applicants respectfully traverse the rejection.

The Examiner has rejected Claim 16 in paragraph 9 on the basis that the scope of the claim on the dosage of IFN is inappropriate. Justification of the use of "units per day" have been already mentioned. Furthermore, justification of the scope of the claim will be described below.

Since development of disease conditions differ among patients, dosages of a medicine should be adjusted depending on the disease condition of a patient. For example, a clinical doctor would provide a preventive treatment to a patient for osteoporosis when the patient has recently experienced menopause and onset of osteoporosis may be expected in the near future. On the other hand, if many days have passed after menopause and the patient repeatedly suffers bone fractures, the doctor gives the patient a therapeutic medication. Various conditions such as side effects and metabolic rates of a medicine that may differ among the patients should be considered for medication. In other words, the optimum dosage of a medicine should be determined by doctor based upon a balance of the risks and benefits after the doctor has interviewed the patient. But this is a common practice for a

clinical doctor. Accordingly, the range of dosage defined in Claim 16 should not be regarded as inappropriate, and the Examiner's observation that undue experimentation is needed is not justified.

Thus, there is considerable direction and guidance in the specification, there is a high level of skill in the art at the time the application was filed, and all the methods needed to practice the invention are well known. Therefore, Applicants respectfully submit the test of enablement has been met, i.e., that one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Please note that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 18 USPQ2d 1331, 1332, (Fed. Cir. 1991).

The fact that some experimentation is required is not fatal, so long as an undue amount is not required. *In re Geerdes*, (CCPA 1974) 180 USPQ 789.

Thus, in view of the comments above, Applicants respectfully request the rejection be withdrawn

Issues Under 35 USC 102

(A) Claim 14 stands rejected under 35 USC 102(b) as being anticipated by Rodriguiz et al (Pediatric Research, 1993, Vol. 33, pp. 384-389). Applicants respectfully traverse the rejection.

In describing the requirements for rejection of a claim by anticipation, the Manual of Patent Examining Procedure (Section 2131) states:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (ref. omitted). The identical invention must be shown in as complete detail as is contained in the... claim (ref. omitted)."

Applicants respectfully submit that Rodriguiz et al does not anticipate claim 14, as presently amended, since Rodriguiz et al fail to teach the use of either interferon β or an interferon β inducer. Also, Rodriguiz et al do not teach the treatment of any disease/disorder currently listed in present claim 14. Accordingly, Rodriguiz et al do not anticipate claim 14, and withdrawal of the rejection is respectfully requested.

(B) Claim 16 stands rejected under 35 USC 102(b) as being anticipated by DelBianco and Sica (USP 5,024,833). Applicants respectfully traverse the rejection.

Applicants respectfully submit that DelBianco and Sica have proved the antitumor action of IFN, not the therapeutic action of IFN for bone diseases. While the Examiner has tried to combine the antitumor action with the therapeutic action for bone diseases on the basis that breast carcinoma often metastasize to the bone, it seems that the Examiner is trying to give a forced interpretation. DelBianco and Sica have restricted the method for evaluating the antitumor effect of IFN to the measurement of the tumor size using X-ray or ultrasonic waves (column 5, lines 4 to 8). The monitoring of bone volume changes is not described anywhere in the patent. This fact clearly indicates that DelBianco and Sica have not been conscious of the action of IFN for altering the bone volume at all, and that DelBianco and Sica have not presented any evidence that may serve as an analogous art for the present invention.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Incidentally, it should be noted that US '833 does not use the expression of "units per kg". The definition of the unit of dosage of IFN that may be conjectured from the specification by DelBianco and Sica is the same definition of "units per day" as used in the present claims.

Issues Under 35 USC 103(a)

(A) Claim 14 stands rejected under 35 USC 103(a) as being unpatentable over Brandely and Lando US 5268169 or Ammann US 4944941 or Sherwin US 4851219 or Adolf US 4791101 in view of Roodman (Calcified Tissue International, 1993). Applicants respectfully traverse the rejections.

Based upon the Examiner's comments, it appears that the Examiner is rejecting claim 14 based upon the interpretation that claim 14 encompasses an embodiment wherein interferon gamma is the sole active agent.

In response, Applicants have amended claim 14 to recite that interferon beta is an active agent. Accordingly, Applicants respectfully request that the rejections be withdrawn.

(B) Claim 15 stands rejected under 35 USC 103(a) as being unpatentable over Brandely and Lando US 5268169 or Ammann US 4944941 or Sherwin US 4851219 or Adolf US 4791101 in view of Fujii et al (Calcified Tissue International, 1990). Applicants respectfully traverse the rejections.

The patents by Brandely and Lando, Ammann and Sherwin show the antitumor action of IFN-γ, and the patent by Adolf show the antitumor action caused by using IFN-β and IFN-γ together. Since the bone diseases are neither described nor suggested in these patents, it is clear that the inventors of the cited patents have not been conscious of the therapeutic effects of IFNs for bone diseases. It is true that Fujii at al suggested possible *in vivo* action of IFN-γ for inhibiting bone resorption in their report. However, contradictory facts have been observed *in vivo* (Rodriguiz, R. M. at al., Pediatrics Res., 33, 384, 1993). Therefore, the present Inventors have been suspicious of the action of IFN-γ reported by Fujii et al as described in the specification of the present invention, and have performed some experiments. In conclusion, the assertions by Fujii at al are erroneous, and Applicants respectfully submit that it is not

proper to reject Claim 15 based on the descriptions in the literature cited above.

Applicants conclude that the reason of rejection by the Examiner is ascribed to confusion of the antitumor action of IFNs with the therapeutic action of IFNs for bone diseases. IFNs have a variety of physiological actions other than those described above, and all the physiological actions are not exerted by administration of the same level of dosage. Accordingly, it is not proper to deny patentability of each of the actions of the IFN as readily conjectured, based on the concept that IFN can induce all these actions by *in vivo* administration.

Based upon the Examiner's comments, it appears that the Examiner is rejecting claim 15 based upon the interpretation that claim 15 encompasses an embodiment wherein interferon gamma is the sole active agent.

In response, Applicants have amended claim 15 to recite that interferon beta is an active agent. Accordingly, Applicants respectfully request that the rejections be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, the invention as instantly claimed is in condition for allowance. A Notice to such effect is earnestly solicited.

In the event there are any additional matters remaining in this application, the Examiner is strongly encouraged to contact Garth M. Dahlen, Ph.D. (Registration #43,575), at (703) 205-8000 in order to discuss these matters.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $890.00 is attached hereto.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this concurrent and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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599-158P
Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend the claims as follows:

Claim 13. (Twice Amended)

A method for treating a patient having an osteoclast related bone disorder comprising administering an effective [an osteoclast related bone disorder treating] amount of interferon β or an interferon β inducer to reinstate bone volume of the patient; wherein the bone disorder results from a disturbance between the relative balance of bone resorption and bone formation[, and

wherein the bone disorder is not rheumatoid arthritis;

wherein when the interferon inducer is interferon γ, the bone disorder is not Paget's disease, osteoporosis, or osteopetrosis; and

wherein when said osteoclast related bone disorder is tumor-related, the tumor-related bone disorder is selected from the group consisting of multiple myeloma, bone metastasis from mammary carcinoma, lung cancer, prostate cancer, thyroid gland carcinoma, renal cancer, colon cancer, cancer of the digestive tract, and cancer of the esophagus].

Claim 14. (Twice Amended)

The method for treating a patient having an osteoclast related bone disorder according to claim 13, wherein the [osteoclast related bone] disorder is selected from the group consisting of rheumatoid arthritis, Paget's disease, rickets, osteoporosis, metabolic disorder, bone fracture, osteomalacia, [osteopetrosis,] osteoarthritis, osteogenesis imperfecta, diseases related to hormonal disorders, autoimmune disorders and periodontal diseases.

Claims 17-21 have been added.